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Draft Guidance on Pegcetacoplan

December 2025

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Active Ingredient:	Pegcetacoplan
Dosage Form:	Solution
Route:	Subcutaneous
Strength:	1080 mg/20 mL (54 mg/mL)
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements and comparative characterization studies to support active ingredient sameness

Waiver of in vivo bioequivalence study requirements:

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b)(1), a generic pegcetacoplan subcutaneous solution product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

An applicant may seek approval of a drug product intended for parenteral use that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the test product.[3]

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the RLD.
[3] 21 CFR 314.94(a)(9)(iii).

Recommendations to Support Active Ingredient Sameness and Impurity Assessment

In addition to ensuring active ingredient sameness (i.e., same primary sequence and physicochemical properties) for the drug substance, it is recommended to conduct the following comparative analyses of the proposed generic pegcetacoplan and the designated reference standard (RS) on no less than three batches of the proposed drug product tested on or near release and at the end of the proposed shelf life and no less than three batches of the RS aged prior to expiry, after aging under conditions consistent with the label storage conditions:[4]

1. Secondary structure.
2. Oligomer/aggregation states: oligomer/aggregation propensity and the nature of the aggregates formed for the proposed product should be similar to that of the RS.
3. Biological activities[5].
4. Active ingredient-related impurity profile comparison: new impurities found in the proposed generic drug product but not in the RS and impurities found at a significantly higher level in the proposed generic drug product than in the RS, should be identified and characterized. If upon Agency assessment, an impurity is identified that has the potential to increase the immunogenicity risk, further immunogenicity assessments or studies may be recommended.
5. Comparative study demonstrating comparable innate immune response risk of the test product and RS.[6]

Non-clinical methods can be used to demonstrate comparable safety and efficacy profiles between a proposed generic peptide (recombinant or synthetically produced) and the RS. Unlike synthetic peptides, recombinant peptides may also contain impurities, such as host cell proteins and residual DNA, from the host cell. Therefore, FDA recommends that applicants demonstrate and justify these host cell related impurities are well controlled if the proposed generic peptide product is manufactured using a recombinant process.[7]

[4] Samples should be aged under conditions consistent with the worst-case label storage conditions.

[5] An applicant may provide justification for not characterizing biological activities as part of the comparative analyses if it can be demonstrated the formulated peptide active ingredient lacks functional secondary or higher order structure.

[6] Demonstrating comparable innate immune activities can be accomplished through analyzing aggregates and non-peptide process-related impurities, which may alter the product's immunogenicity profile. Differences found in comparability studies assessing aggregates should be mitigated using manufacturing strategies. Levels of non-peptide process-related impurities including particulate matter, microbial contaminants, residual organic solvents, elemental impurities and leachables, should meet compendial acceptance criteria and toxicological limits. If non-peptide process-related impurities meet these criteria and limits, and aggregation profiles are comparable to that of the RS, applicants should not conduct in vitro innate immune testing.

[7] For any inquiries regarding the use of non-clinical assays to assess risk in recombinant generic peptides, submit pre-ANDA product development meeting requests. For additional information, refer to the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA.*

Additional information:

Device:
The RLD is presented in a single-dose vial for administration with a commercially available infusion pump with a reservoir of at least 20 mL or with the EMPAVELI on-body injector. The RLD is a drug-device combination product, and the EMPAVELI on-body injector is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- Single-use, on-body injector format
- Dose delivery profile
- Needle gauge, length, and safety features

User interface assessment:
An abbreviated new drug application for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.